Epithelial progenitors and the stromal niche as therapeutic targets in lung disease

Grant Award Details

Epithelial progenitors and the stromal niche as therapeutic targets in lung disease

Grant Type: Research Leadership

Grant Number: LA1-06915

Project Objective: The general goal of this research program is to identify determinants of lung epithelial maintenance and repair so that they might be exploited for therapeutic purposes. Sub-objectives are to a) test hypothesis that disruption of cellular communications between epithelial progenitors and their surroundings lead to lung disease such as idiopathic pulmonary fibrosis (IPF) and bronchiolitis obliterans syndrome (BOS); and b) establish efficient methods for deriving bronchiolar and/or alveolar progenitors from hPSCs for patient-specific drug screens and therapeutic applications.

Investigator:

Name:	Barry Stripp
Institution:	Cedars-Sinai Medical Center
Type:	PI

Disease Focus: Respiratory Disorders

Human Stem Cell Use: iPS Cell

Cell Line Generation: Adult Stem Cell, iPS Cell

Award Value: $4,841,830

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Epithelial progenitors and the stromal niche as therapeutic targets in lung disease

Public Abstract: Chronic lung disease is an enormous societal and medical problem in California and the nation as a whole, representing the third most likely cause of death. Treatment costs were $389.2 billion in 2011 and are expected to reach $832.9 billion in 2021 according to the Milken Institute. Chronic lung diseases cover a spectrum of disorders that include pulmonary fibrosis, a disease that makes it difficult to breathe due to the accumulation of scar tissue in the lung, and chronic obstructive pulmonary disease (COPD), a disease that makes breathing difficult due to loss of critical structures that allow oxygen to enter the blood. According to Breathe California, COPD is the 4th leading cause of death in the United States and 1.6 million Californians are diagnosed with COPD. Treatment options vary by disease but are particularly ineffective for patients with COPD and fibrotic lung diseases. One fibrotic lung disease termed idiopathic pulmonary fibrosis (IPF) can only be treated by lung transplantation and this option is limited to those who meet specific age and health criteria. Without transplantation the majority of IPF patients die within three years of initial diagnosis.

Our research team being recruited to California is led by an international expert in lung stem cell biology and includes a leading physician in pulmonary fibrosis research and clinical management. Goals of research outlined in this proposal are to understand how lungs are damaged by diseases and to develop new treatment options to help prevent, arrest, or repair damage leading to improved patient health. Specifically, we will show how cells that line airspaces of the lung generate new cells that function to protect the lung from injury and facilitate gas exchange during breathing. Through this work it will be possible to determine how lung disease is caused and this will lead to new therapies that will prevent either initiation or progression of lung disease.

Statement of Benefit to California:

Lung disease has an enormous societal impact. For the period from 1990-2008 chronic lower respiratory diseases were the third most likely cause of death in the US, accounting for approximately 6% of deaths and an annual rate of approximately 0.1% of the total population (NHLBI report, 2010). Lung diseases can be caused by either genetic and/or environmental factors, and are
compounded by age-related declines in lung function. Poor air quality in and around major California cities are well documented and have been conservatively estimated to account for 10,000 hospital visits per year (RAND Corporation report, 2010). Ozone and particulate airborne pollutants are a significant concern due to chronic effects on lung tissue remodeling in otherwise healthy individuals. They also trigger exacerbations in patients with existing lung disease leading to more serious illness and death. Interventions can include imposing strict air quality standards and improving therapies for patients either with or who are at risk of developing lung disease. Pulmonary fibrosis in particular represents a major unmet medical need in California and lung transplant is the only effective therapy at present. Accordingly, defining mechanisms of lung fibrosis and developing cures for otherwise intractable lung diseases has the potential to significantly benefit the population of California.

This CIRM Research Leadership Award application will develop a transformative program aimed at applying new discoveries in basic mechanisms of lung disease towards development of new interventions to help patients. This will be accomplished by integrating the applicant's expertise in lung stem cell biology and regenerative medicine with basic and translational research strengths at the destination institution. Previous work has shown that signaling interactions between epithelial progenitor cells and their associated stromal microenvironment are critical for normal development and tissue homeostasis in adulthood. These interactions are dysregulated in many lung diseases including fibrotic lung diseases, chronic obstructive pulmonary disease and asthma. This proposal will focus on fibrotic lung diseases in particular due to the poor prognosis that results from lack of effective therapies. Through identifying mediators that regulate epithelial progenitor-stromal interactions in the normal adult lung, and how changes in their activity contribute to disease, we will gain new insights into disease mechanisms and therapies. We expect that discoveries will be broadly applicable to many lung diseases and will significantly impact Californians through
novel drug discoveries that improve the health and quality of life of patients with early onset or established lung disease.
